

NDA 20-068/S-013
NDA 20-068/S-014

JUN 13 2000

AstraZeneca LP
Attention: Lisa DeLuca, PhD
Regulatory Liaison Director
725 Chesterbrook Boulevard
Wayne, PA 19087-5677

Dear Dr. DeLuca:

Please refer to your supplemental new drug applications dated August 25, 1998 (S-013) and August 27, 1999 (S-014) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FOSCAVIR (foscarnet sodium) Injection.

We acknowledge receipt of your submissions dated September 15, 1999, December 16, 1999, March 15, 2000 and June 1, 2000.

The submission dated June 1, 2000 provides for changing the following under the **PRECAUTIONS** section, **Drug Interactions** subsection:

“Abnormal renal function has been observed in clinical practice during the use of FOSCAVIR and ritonavir or FOSCAVIR, ritonavir, and saquinavir.(See DOSAGE and ADMINISTRATION.)”

In addition, we &knowledge that the word “children” has been changed to “pediatric patients” in the **PRECAUTIONS** section under **the Pediatric Use** subsection.

The submission dated June 1, 2000 provides for changing the following under the **PRECAUTIONS** section, **Geriatric Use** subsection:

“No studies of the efficacy or safety of FOSCAVIR in persons 65 years of age or older have been conducted. However, FOSCAVIR has been used in patients age 65 years of age and older. The pattern of adverse events seen in these patients is consistent across all age groups. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored. (See DOSAGE AND ADMINISTRATION.)”

NDA 20-068/S-01 3
NDA 20-068/S-014
Page 2

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text, dated June 1, 2000. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (text for the package insert) submitted June 1, 2000.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavyweight paper or similar material.

For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20068/S-013 and S-014." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Leslie Stephens, R.N., M.S.N., Regulatory Project Manager, at (301) 827-2335.

Sincerely yours,

FOSCAVIR®

(foscarnet sodium) Injection

WARNING

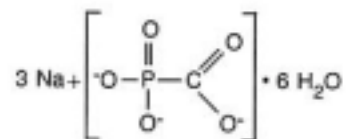
RENAL IMPAIRMENT IS THE MAJOR TOXICITY OF FOSCAVIR. FREQUENT MONITORING OF SERUM CREATININE, WITH DOSE ADJUSTMENT FOR CHANGES IN RENAL FUNCTION, AND ADEQUATE HYDRATION WITH ADMINISTRATION OF FOSCAVIR, IS IMPERATIVE. (See ADMINISTRATION section; Hydration.)

SEIZURES, RELATED TO ALTERATIONS IN PLASMA MINERALS AND ELECTROLYTES, HAVE BEEN ASSOCIATED WITH FOSCAVIR TREATMENT. THEREFORE, PATIENTS MUST BE CAREFULLY MONITORED FOR SUCH CHANGES AND THEIR POTENTIAL SEQUELAE. MINERAL AND ELECTROLYTE SUPPLEMENTATION MAY BE REQUIRED.

FOSCAVIR IS INDICATED FOR USE ONLY IN IMMUNOCOMPROMISED PATIENTS WITH CMV RETINITIS AND MUCOCUTANEOUS ACYCLOVIR-RESISTANT HSV INFECTIONS. (See INDICATIONS section.)

DESCRIPTION

FOSCAVIR is the brand name for foscarnet sodium. The chemical name of foscarnet sodium is phosphonoformic acid, trisodium salt. Foscarnet sodium is a white, crystalline powder containing 6 equivalents of water of hydration with an empirical formula of $\text{Na}_3\text{CO}_5\text{P} \cdot 6\text{H}_2\text{O}$ and a molecular weight of 300.1. The structural formula is:



FOSCAVIR has the potential to chelate divalent metal ions, such as calcium and magnesium, to form stable coordination compounds. FOSCAVIR INJECTION is a sterile, isotonic aqueous solution for intravenous administration only. The solution is clear and colorless. Each milliliter of FOSCAVIR contains 24 mg of foscarnet sodium hexahydrate in Water for Injection, USP. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH of the solution to 7.4. FOSCAVIR INJECTION contains no preservatives.

VIROLOGY

Mechanism of Action: FOSCAVIR is an organic analogue of inorganic pyrophosphate that inhibits replication of herpesviruses *in vitro* including cytomegalovirus (CMV) and herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).

FOSCAVIR exerts its antiviral activity by a selective inhibition at the pyrophosphate binding site on virus-specific DNA polymerases at concentrations that do not affect cellular DNA polymerases. FOSCAVIR does not require activation (phosphorylation) by thymidine kinase or other kinases and therefore is active *in vitro* against HSV TK deficient mutants and CMV UL97 mutants. Thus, HSV strains resistant to acyclovir or CMV strains resistant to ganciclovir may be sensitive to FOSCAVIR. However, acyclovir or ganciclovir resistant mutants with alterations in the viral DNA polymerase may be resistant to FOSCAVIR and may not respond to therapy with FOSCAVIR. The combination of FOSCAVIR and ganciclovir has been shown to have enhanced activity *in vitro*.

Antiviral Activity *in vitro* and *in vivo*: The quantitative relationship between the *in vitro* susceptibility of human cytomegalovirus (CMV) or herpes simplex virus 1 and 2 (HSV-1 and HSV-2) to FOSCAVIR and clinical response to therapy has not been established and virus sensitivity testing has not been standardized. Sensitivity test results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending on the assay method used, cell type employed and the laboratory performing the test. A number of sensitive viruses and their IC_{50} values are listed below (Table 1).

TABLE 1
FOSCARNET Inhibition of virus multiplication in cell culture

Virus	IC ₅₀ (μ M)
CMV	50-800 *
HSV-1, HSV-2	10-130
Ganciclovir resistant CMV	190
HSV-TK negative mutant	67
HSV-DNA polymerase mutants	5-443
* Mean = 269 μ M	

Statistically significant decreases in positive CMV cultures from blood and urine have been demonstrated in two studies (FOS-03 and ACTG-015/915) of patients treated with FOSCAVIR. Although median time to progression of CMV retinitis was increased in patients treated with FOSCAVIR, reductions in positive blood or urine cultures have not been shown to correlate with clinical efficacy in individual patients.

TABLE 2
BLOOD AND URINE CULTURE RESULTS FROM CMV RETINITIS PATIENTS *

	+CMV	-CMV
Blood		
Baseline	27	34
End of Induction **	1	60
Urine		
Baseline	52	6
End of Induction **	21	37

* A total of 77 patients was treated with FOSCAVIR in two clinical trials (FOS-03 and ACTG-015/915). Not all patients had blood or urine cultures done and some patients had results from both cultures.

** (60 mg/kg FOSCAVIR TID for 2-3 weeks).

Resistance: Strains of both HSV and CMV that are resistant to FOSCAVIR can be readily selected *in vitro* by passage of wild type virus in the presence of increasing concentrations of the drug. All FOSCAVIR resistant mutants are known to be generated through mutation in the viral DNA polymerase gene. CMV strains with double mutations conferring resistance to both FOSCAVIR and ganciclovir have been isolated from patients with AIDS. The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

CLINICAL PHARMACOLOGY

Pharmacokinetics: The pharmacokinetics of foscarnet have been determined after administration as an intermittent intravenous infusion during induction therapy in AIDS patients with CMV retinitis. Observed plasma foscarnet concentrations in four studies (FOS-01, ACTG-015, FP48PK, FP49PK) are summarized in Table 3:

TABLE 3
Foscarnet Pharmacokinetic Characteristics *

Parameter	60 mg/kg Q8h	90 mg/kg Q12h
C_{max} at steady-state (μ M)	589 ± 192 (24)	623 ± 132 (19)
C_{trough} at steady-state (μ M)	114 ± 91 (24)	63 ± 57 (17)
Volume of distribution (L/kg)	0.41 ± 0.13 (12)	0.52 ± 0.20 (18)
Plasma half-life (hr)	4.0 ± 2.0 (24)	3.3 ± 1.4 (18)
Systemic clearance (L/hr)	6.2 ± 2.1 (24)	7.1 ± 2.7 (18)
Renal clearance (L/hr)	5.6 ± 1.9 (5)	6.4 ± 2.5 (13)
CSF:plasma ratio	0.69 ± 0.19 (9) **	0.66 ± 0.11 (5) ***

* Values expressed as mean ± S.D. (number of subjects studied) for each parameter

** 50 mg/kg Q8h for 28 days, samples taken 3 hrs after end of 1 hr infusion (Astra Report 815-04 AC025-1)

*** 90 mg/kg Q12h for 28 days, samples taken 1 hr after end of 2 hr infusion (Hengge et al., 1993)

Distribution: *In vitro* studies have shown that 14-17% of foscarnet is protein bound at plasma drug concentrations of 1-1000 μ M.

The foscarnet terminal half-life determined by urinary excretion was 87.5 ± 41.8 hours, possibly due to release of foscarnet from bone. Postmortem data on several patients in European clinical trials provide evidence that foscarnet does accumulate in bone in humans; however, the extent to which this occurs has not been determined. In animal studies (mice), 40% of an intravenous dose of FOSCAVIR was deposited in bone in young animals and 7% was deposited in adult animals.

Special Populations:

Adults with Impaired Renal Function --The pharmacokinetic properties of foscarnet have been determined in a small group of adult subjects with normal and impaired renal function, as summarized in Table 4:

TABLE 4
Pharmacokinetic Parameters (mean ± S.D.) After a Single 60 mg/kg Dose of FOSCAVIR in 4 Groups * of Adults with Varying Degrees of Renal Function

Parameter	Group 1 (N=6)	Group 2 (N=6)	Group 3 (N=6)	Group 4 (N=4)
Creatinine clearance (mL/min)	108 ± 16	68 ± 8	34 ± 9	20 ± 4
Foscarnet CL (mL/min/kg)	2.13 ± 0.71	1.33 ± 0.43	0.46 ± 0.14	0.43 ± 0.26
Foscarnet half-life (hr)	1.93 ± 0.12	3.35 ± 0.87	13.0 ± 4.05	25.3 ± 18.7

* Group 1 patients had normal renal function defined as a creatinine clearance (CrCl) of >80 mL/min, Group 2 CrCl was 50-80 mL/min, Group 3 CrCl was 25-49 mL/min and Group 4 CrCl was 10-24 mL/min.

Total systemic clearance (CL) of foscarnet decreased and half-life increased with diminishing renal function (as expressed by creatinine clearance). Based on these observations, it is necessary to modify the dosage of foscarnet in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

CMV Retinitis: A prospective, randomized, controlled clinical trial (FOS-03) was conducted in 24 patients with AIDS and CMV retinitis comparing treatment with FOSCAVIR to no treatment. Patients received induction treatment of FOSCAVIR, 60 mg/kg every 8 hours for 3 weeks, followed by maintenance treatment with 90 mg/kg/day until retinitis progression (appearance of a new lesion or advancement of the border of a posterior lesion greater than 750 microns in diameter). All diagnoses and determinations of retinitis progression were made from masked reading of retinal photographs. The 13 patients randomized to treatment with FOSCAVIR had a significant delay in progression of CMV retinitis compared to untreated controls. Median times to retinitis progression from study entry were 93 days (range 21- >364) and 22 days (range 7-42), respectively.

In another prospective clinical trial of CMV retinitis in patients with AIDS (ACTG-915), 33 patients were treated with two to three weeks of FOSCAVIR induction (60 mg/kg TID) and then randomized to either 90 mg/kg/day or 120 mg/kg/day maintenance therapy. The median times from study entry to retinitis progression were not significantly different between the treatment groups, 96 (range 14- >176) days and 140 (range 16- >233) days, respectively.

In study ACTG 129/FGCRT SOCA study 107 patients with newly diagnosed CMV retinitis were randomized to treatment with FOSCAVIR (induction: 60 mg/kg TID for 2 weeks; maintenance: 90 mg/kg QD) and 127 were randomized to treatment with ganciclovir (induction: 5 mg/kg BID; maintenance: 5 mg/kg QD). The median time to progression on the two drugs was similar (Fos=59 and Gcv=56 days).

Relapsed CMV Retinitis: The CMV Retinitis Retreatment Trial (ACTG 228/SOCA CRRT) was a randomized, open-label comparison of FOSCAVIR or ganciclovir monotherapy to the combination of both drugs for the treatment of persistently active or relapsed CMV retinitis in patients with AIDS. Subjects were randomized to one of the three treatments: FOSCAVIR 90 mg/kg BID induction followed by 120 mg/kg QD maintenance (Fos); ganciclovir 5 mg/kg BID induction followed by 10 mg/kg QD maintenance (Gcv); or the combination of the two drugs, consisting of continuation of the subject's current therapy and induction dosing of the other drug (as above), followed by maintenance with FOSCAVIR 90 mg/kg QD plus ganciclovir 5 mg/kg QD (Cmb). Assessment of retinitis progression was performed by masked evaluation of retinal photographs. The median times to retinitis progression or death were 39 days for the FOSCAVIR group, 61 days for the ganciclovir group and 105 days for the combination group. For the alternative endpoint of retinitis progression (censoring on death), the median times were 39 days for the FOSCAVIR group, 61 days for the ganciclovir group and 132 days for the combination group. Due to censoring on death, the latter analysis may overestimate the treatment effect. Treatment modifications due to toxicity were more common in the combination group than in the FOSCAVIR or ganciclovir monotherapy groups (see ADVERSE REACTIONS section).

Mucocutaneous Acyclovir-Resistant HSV Infections: In a controlled trial, patients with AIDS and mucocutaneous, acyclovir-resistant HSV infection were randomized to either FOSCAVIR (N=8) at a dose of 40 mg/kg TID or vidarabine (N=6) at a dose of 15 mg/kg per day. Eleven patients were non-randomly assigned to receive treatment with FOSCAVIR because of prior intolerance to vidarabine. Lesions in the eight patients randomized to FOSCAVIR healed after 11 to 25 days; seven of the 11 patients non-randomly treated with FOSCAVIR healed their lesions in 10 to 30 days. Vidarabine was discontinued because of intolerance (N=4) or poor therapeutic response (N=2). In a second trial, forty AIDS patients and three bone marrow transplant recipients with mucocutaneous, acyclovir-resistant HSV infections were randomized to receive FOSCAVIR at a dose of either 40 mg/kg BID or 40 mg/kg TID. Fifteen of the 43 patients had healing of their lesions in 11 to 72 days with no difference in response between the two treatment groups.

INDICATIONS

CMV Retinitis: FOSCAVIR is indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). Combination therapy with FOSCAVIR and ganciclovir is indicated for patients who have relapsed after monotherapy with either drug. SAFETY AND EFFICACY OF FOSCAVIR HAVE NOT BEEN ESTABLISHED FOR TREATMENT OF OTHER CMV INFECTIONS (e.g., PNEUMONITIS, GASTROENTERITIS); CONGENITAL OR NEONATAL CMV DISEASE; OR NON-IMMUNOCOMPROMISED INDIVIDUALS.

Mucocutaneous Acyclovir-Resistant HSV Infections: FOSCAVIR is indicated for the treatment of acyclovir-resistant mucocutaneous HSV infections in immunocompromised patients. SAFETY AND EFFICACY OF FOSCAVIR HAVE NOT BEEN ESTABLISHED FOR TREATMENT OF OTHER HSV INFECTIONS (e.g.,

RETINITIS, ENCEPHALITIS); CONGENITAL OR NEONATAL HSV DISEASE; OR HSV IN NON-IMMUNOCOMPROMISED INDIVIDUALS.

CONTRAINDICATIONS

FOSCAVIR is contraindicated in patients with clinically significant hypersensitivity to foscarnet sodium.

WARNINGS

Renal Impairment: THE MAJOR TOXICITY OF FOSCAVIR IS RENAL IMPAIRMENT (see ADVERSE REACTIONS section). Renal impairment is most likely to become clinically evident during the second week of induction therapy, but may occur at any time during FOSCAVIR treatment. Renal function should be monitored carefully during both induction and maintenance therapy (see PATIENT MONITORING section). Elevations in serum creatinine are usually, but not always, reversible following discontinuation or dose adjustment of FOSCAVIR. Safety and efficacy data for patients with baseline serum creatinine levels greater than 2.8 mg/dL or measured 24-hour creatinine clearances <50 mL/min are limited.

BECAUSE OF FOSCAVIR'S POTENTIAL TO CAUSE RENAL IMPAIRMENT, DOSE ADJUSTMENT BASED ON SERUM CREATININE IS NECESSARY. Hydration may reduce the risk of nephrotoxicity. It is recommended that 750-1000 mL of normal saline or 5% dextrose solution should be given prior to the first infusion of FOSCAVIR to establish diuresis. With subsequent infusions, 750-1000 mL of hydration fluid should be given with 90-120 mg/kg of FOSCAVIR, and 500 mL with 40-60 mg/kg of FOSCAVIR. Hydration fluid may need to be decreased if clinically warranted.

After the first dose, the hydration fluid should be administered concurrently with each infusion of FOSCAVIR.

Mineral and Electrolyte Abnormalities: FOSCAVIR has been associated with changes in serum electrolytes including hypocalcemia, hypophosphatemia, hyperphosphatemia, hypomagnesemia, and hypokalemia (see ADVERSE REACTIONS section). FOSCAVIR may also be associated with a dose-related decrease in ionized serum calcium which may not be reflected in total serum calcium. This effect is likely to be related to chelation of divalent metal ions such as calcium by foscarnet. Patients should be advised to report symptoms of low ionized calcium such as perioral tingling, numbness in the extremities and paresthesias. Particular caution and careful management of serum electrolytes is advised in patients with altered calcium or other electrolyte levels before treatment and especially in those with neurologic or cardiac abnormalities and those receiving other drugs known to influence minerals and electrolytes (see PATIENT MONITORING and Drug Interactions sections). Physicians should be prepared to treat these abnormalities and their sequelae such as tetany, seizures or cardiac disturbances. The rate of FOSCAVIR infusion may also affect the decrease in ionized calcium. **Therefore, an infusion pump must be used for administration to prevent rapid intravenous infusion (see DOSAGE AND ADMINISTRATION section).** Slowing the infusion rate may decrease or prevent symptoms.

Seizures: Seizures related to mineral and electrolyte abnormalities have been associated with FOSCAVIR treatment (see WARNING section; Mineral and Electrolyte Abnormalities). Several cases of seizures were associated with death. Risk factors associated with seizures included impaired baseline renal function, low total serum calcium, and underlying CNS conditions.

PRECAUTIONS

General: Care must be taken to infuse solutions containing FOSCAVIR only into veins with adequate blood flow to permit rapid dilution and distribution to avoid local irritation (see DOSAGE AND ADMINISTRATION). Local irritation and ulcerations of penile epithelium have been reported in male patients receiving FOSCAVIR, possibly related to the presence of drug in the urine. One case of vulvovaginal ulcerations in a female receiving FOSCAVIR has been reported. Adequate hydration with close attention to personal hygiene may minimize the occurrence of such events.

Hemopoietic System: Anemia has been reported in 33% of patients receiving FOSCAVIR in controlled studies. Granulocytopenia has been reported in 17% of patients receiving FOSCAVIR in controlled studies; however, only 1% (2/189) were terminated from these studies because of neutropenia.

Information for Patients

CMV Retinitis --Patients should be advised that FOSCAVIR is not a cure for CMV retinitis, and that they may continue to experience progression of retinitis during or following treatment. They should be advised to have regular ophthalmologic examinations.

Mucocutaneous Acyclovir-Resistant HSV Infections --Patients should be advised that FOSCAVIR is not a cure for HSV infections. While complete healing is possible, relapse occurs in most patients. Because relapse may be due to acyclovir-sensitive HSV, sensitivity testing of the viral isolate is advised. In addition, repeated treatment with FOSCAVIR has led to the development of resistance associated with poorer response. In the case of poor therapeutic response, sensitivity testing of the viral isolate also is advised.

General --Patients should be informed that the major toxicities of foscarnet are renal impairment, electrolyte disturbances, and seizures, and that dose modifications and possibly discontinuation may be required. The importance of close monitoring while on therapy must be emphasized. Patients should be advised of the importance of reporting to their physicians symptoms of perioral tingling, numbness in the extremities or paresthesias during or after infusion as possible symptoms of electrolyte abnormalities. Should such symptoms occur, the infusion of FOSCAVIR should be stopped, appropriate laboratory samples for assessment of electrolyte concentrations obtained, and a physician consulted before resuming treatment. The rate of infusion must be no more than 1 mg/kg/minute. The potential for renal impairment may be minimized by accompanying FOSCAVIR administration with hydration adequate to establish and maintain a diuresis during dosing.

Drug Interactions: A possible drug interaction of FOSCAVIR and intravenous pentamidine has been described. Concomitant treatment of four patients in the United Kingdom with FOSCAVIR and intravenous pentamidine may have caused hypocalcemia; one patient died with severe hypocalcemia. Toxicity associated with concomitant use of aerosolized pentamidine has not been reported.

Because of foscarnet's tendency to cause renal impairment, the use of FOSCAVIR should be avoided in combination with potentially nephrotoxic drugs such as aminoglycosides, amphotericin B and intravenous pentamidine (see above) unless the potential benefits outweigh the risks to the patient.

Abnormal renal function has been observed in clinical practice during the use of FOSCAVIR and ritonavir or FOSCAVIR, ritonavir, and saquinavir. (See DOSAGE AND ADMINISTRATION.)

Since FOSCAVIR decreases serum concentrations of ionized calcium, concurrent treatment with other drugs known to influence serum calcium concentrations should be used with particular caution.

Ganciclovir --The pharmacokinetics of foscarnet and ganciclovir were not altered in 13 patients receiving either concomitant therapy or daily alternating therapy for maintenance of CMV disease.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies were conducted in rats and mice at oral doses of 500 mg/kg/day and 250 mg/kg/day. Oral bioavailability in unfasted rodents is < 20%. No evidence of oncogenicity was reported at plasma drug levels equal to 1/3 and 1/5, respectively, of those in humans (at the maximum recommended human daily dose) as measured by the area-under-the-time/concentration curve (AUC). FOSCAVIR showed genotoxic effects in the BALB/3T3 *in vitro* transformation assay at concentrations greater than 0.5 mcg/mL and an increased frequency of chromosome aberrations in the sister chromatid exchange assay at 1000 mcg/mL. A high dose of foscarnet (350 mg/kg) caused an increase in micronucleated polychromatic erythrocytes *in vivo* in mice at doses that produced exposures (area under curve) comparable to that anticipated clinically.

Pregnancy: Teratogenic Effect:

Pregnancy, Category C: FOSCAVIR did not adversely affect fertility and general reproductive performance in rats. The results of peri- and post-natal studies in rats were also negative. However, these studies used exposures that are inadequate to define the potential for impairment of fertility at human drug exposure levels.

Daily subcutaneous doses up to 75 mg/kg administered to female rats prior to and during mating, during gestation, and 21 days post-partum caused a slight increase (< 5%) in the number of skeletal anomalies compared with the control group. Daily subcutaneous doses up to 75 mg/kg administered to rabbits and 150 mg/kg administered to rats during gestation caused an increase in the frequency of skeletal anomalies/variations. On the basis of estimated drug exposure (as measured by AUC), the 150 mg/kg dose in rats and 75 mg/kg dose in rabbits were approximately one-eighth (rat) and one-third (rabbit) the estimated maximal daily human exposure. These studies are inadequate to define the potential teratogenicity at levels to which women will be exposed.

There are no adequate and well controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, FOSCAVIR should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether FOSCAVIR is excreted in human milk; however, in lactating rats administered 75 mg/kg, FOSCAVIR was excreted in maternal milk at concentrations three times higher than peak maternal blood concentrations.

Pediatric Use: The safety and effectiveness of FOSCAVIR in pediatric patients have not been established. FOSCAVIR is deposited in teeth and bone and deposition is greater in young and growing animals. FOSCAVIR has been demonstrated to adversely affect development of tooth enamel in mice and rats. The effects of this deposition on skeletal development have not been studied. Since deposition in human bone has also been shown to occur, it is likely that it does so to a greater degree in developing bone in pediatric patients. Administration to pediatric patients should be undertaken only after careful evaluation and only if the potential benefits for treatment outweigh the risks.

Geriatric Use: : No studies of the efficacy or safety of FOSCAVIR in persons over age 65 have been conducted. However, FOSCAVIR has been used in patients age 65 years of age and older. The pattern of adverse events seen in these patients is consistent across all age groups. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored. (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

THE MAJOR TOXICITY OF FOSCAVIR IS RENAL IMPAIRMENT (see WARNINGS section). Approximately 33% of 189 patients with AIDS and CMV retinitis who received FOSCAVIR (60 mg/kg TID), without adequate hydration, developed significant impairment of renal function (serum creatinine \geq 2.0 mg/dL). The incidence of renal impairment in subsequent clinical trials in which 1000 mL of normal saline or 5% dextrose solution was given with each infusion of FOSCAVIR was 12% (34/280).

FOSCAVIR has been associated with changes in serum electrolytes including hypocalcemia (15-30%), hypophosphatemia (8-26%) and hyperphosphatemia (6%), hypomagnesemia (15-30%), and hypokalemia (16-48%) (see WARNINGS section). The higher percentages were derived from those patients receiving hydration.

FOSCAVIR treatment was associated with seizures in 18/189 (10%) AIDS patients in the initial five controlled studies (see WARNINGS section). Risk factors associated with seizures included impaired baseline renal function, low total serum calcium, and underlying CNS conditions predisposing the patient to seizures. The rate of seizures did not increase with duration of treatment. Three cases were associated with overdoses of FOSCAVIR (see OVERDOSAGE section).

In five controlled U.S. clinical trials the most frequently reported adverse events in patients with AIDS and CMV retinitis are shown in Table 5. These figures were calculated without reference to drug relationship or severity.

TABLE 5--Adverse Events Reported in Five Controlled US Clinical Trials

	n = 189		n = 189
Fever	65%	Abnormal Renal Function	27%
Nausea	47%	Vomiting	26%
Anemia	33%	Headache	26%
Diarrhea	30%	Seizures	10%

From the same controlled studies, adverse events categorized by investigator as "severe" are shown in Table 6. Although death was specifically attributed to FOSCAVIR in only one case, other complications of FOSCAVIR (i.e., renal impairment, electrolyte abnormalities, and seizures) may have contributed to patient deaths (see WARNINGS section).

TABLE 6--Severe Adverse Events

	n = 189
Death	14%
Abnormal Renal Function	14%

Marrow Suppression	10%
Anemia	9%
Seizures	7%

From the five initial U.S. controlled trials of FOSCAVIR, the following list of adverse events has been compiled regardless of causal relationship to FOSCAVIR. Evaluation of these reports was difficult because of the diverse manifestations of the underlying disease and because most patients received numerous concomitant medications.

Incidence 5% or Greater

Body as a Whole: fever, fatigue, rigors, asthenia, malaise, pain, infection, sepsis, death

Central and Peripheral Nervous System: headache, paresthesia, dizziness, involuntary muscle contractions, hypoesthesia, neuropathy, seizures including grand mal seizures (see WARNINGS)

Gastrointestinal System: anorexia, nausea, diarrhea, vomiting, abdominal pain

Hematologic: anemia, granulocytopenia, leukopenia (see PRECAUTIONS)

Metabolic and Nutritional: mineral and electrolyte imbalances (see WARNINGS) including hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia

Psychiatric: depression, confusion, anxiety

Respiratory System: coughing, dyspnea

Skin and Appendages: rash, increased sweating

Urinary: alterations in renal function including increased serum creatinine, decreased creatinine clearance, and abnormal renal function (see WARNINGS)

Special Senses: vision abnormalities

Incidence between 1% and 5%

Application Site: injection site pain, injection site inflammation

Body as a Whole: back pain, chest pain, edema, influenza-like symptoms, bacterial infections, moniliasis, fungal infections, abscess

Cardiovascular: hypertension, palpitations, ECG abnormalities including sinus tachycardia, first degree AV block and non-specific ST-T segment changes, hypotension, flushing, cerebrovascular disorder (see WARNINGS)

Central and Peripheral Nervous System: tremor, ataxia, dementia, stupor, generalized spasms, sensory disturbances, meningitis, aphasia, abnormal coordination, leg cramps, EEG abnormalities (see WARNINGS)

Gastrointestinal: constipation, dysphagia, dyspepsia, rectal hemorrhage, dry mouth, melena, flatulence, ulcerative stomatitis, pancreatitis

Hematologic: thrombocytopenia, platelet abnormalities, thrombosis, white blood cell abnormalities, lymphadenopathy

Liver and Biliary: abnormal A-G ratio, abnormal hepatic function, increased SGPT, increased SGOT

Metabolic and Nutritional: hyponatremia, decreased weight, increased alkaline phosphatase, increased LDH, increased BUN, acidosis, cachexia, thirst, hypercalcemia (see WARNINGS)

Musculo-Skeletal: arthralgia, myalgia

Neoplasms: lymphoma-like disorder, sarcoma

Psychiatric: insomnia, somnolence, nervousness, amnesia, agitation, aggressive reaction, hallucination

Respiratory System: pneumonia, sinusitis, pharyngitis, rhinitis, respiratory disorders, respiratory insufficiency, pulmonary infiltration, stridor, pneumothorax, hemoptysis, bronchospasm

Skin and Appendages: pruritus, skin ulceration, seborrhea, erythematous rash, maculo-papular rash, skin discoloration

Special Senses: taste perversions, eye abnormalities, eye pain, conjunctivitis

Urinary System: albuminuria, dysuria, polyuria, urethral disorder, urinary retention, urinary tract infections, acute renal failure, nocturia, facial edema

Selected adverse events occurring at a rate of less than 1% in the five initial U.S. controlled clinical trials of FOSCAVIR include: syndrome of inappropriate antidiuretic hormone secretion, pancytopenia, hematuria, dehydration, hypoproteinemia, increases in amylase and creatinine phosphokinase, cardiac arrest, coma, and other cardiovascular and neurologic complications.

Selected adverse event data from the Foscarnet vs. Ganciclovir CMV Retinitis Trial (FGCRT), performed by the Studies of the Ocular Complications of AIDS (SOCA) Research Group, are shown in Table 7 (see CLINICAL TRIALS section).

TABLE 7--FGCRT: SELECTED ADVERSE EVENTS *

EVENT	GANCICLOVIR			FOSCARNET		
	No. of Events	No. of Patients	Rates §	No. of Events	No. of Patients	Rates§
Absolute neutrophil count decreasing to $<0.50 \times 10^9$ per liter	63	41	1.30	31	17	0.72
Serum creatinine increasing to >260 μ mol per liter (>2.9 mg/dL)	6	4	0.12	13	9	0.30
Seizure **	21	13	0.37	19	13	0.37
Catheterization-related infection	49	27	1.26	51	28	1.46
Hospitalization	209	91	4.74	202	75	5.03

* Values for the treatment groups refer only to patients who completed at least one follow-up visit--i.e., 113 to 119 patients in the ganciclovir group and 93 to 100 in the foscarnet group. "Events" denotes all events observed and "patients" the number of patients with one or more of the indicated events.

** Final frozen SOCA I database dated October 1991.

§ Per person-year at risk

Selected adverse events from ACTG Study 228 (CRRT) comparing combination therapy with FOSCAVIR or ganciclovir monotherapy are shown in Table 8. The most common reason for a treatment change in patients assigned to either FOSCAVIR or ganciclovir was retinitis progression. The most frequent reason for a treatment change in the combination treatment group was toxicity.

TABLE 8
CRRT: Selected Adverse Events

	Foscavir N=88			Ganciclovir N=93			Combination N=93		
	No. Events	No. Pts. &	Rate #	No. Events	No. Pts. &	Rate #	No. Events	No. Pts. &	Rate #
Anemia (Hgb <70 g/L)	11	7	0.20	9	7	0.14	19	15	0.33
Neutropenia §									
ANC <0.75 × 10 ⁹ cells/L	86	32	1.53	95	41	1.51	107	51	1.91
ANC <0.50 × 10 ⁹ cells/L	50	25	0.91	49	28	0.80	50	28	0.85
Thrombocytopenia									
Platelets <50 × 10 ⁹ /L	28	14	0.50	19	8	0.43	40	15	0.56
Platelets <20 × 10 ⁹ /L	1	1	0.01	6	2	0.05	7	6	0.18
Nephrotoxicity									
Creatinine >260 μ mol/L (>2.9 mg/dL)	9	7	0.15	10	7	0.17	11	10	0.20
Seizures	6	6	0.17	7	6	0.15	10	5	0.18
Hospitalizations	86	53	1.86	111	59	2.36	118	64	2.36

& Pts. = patients with event;

Rate = events/person/year;

§ ANC = absolute neutrophil count

Adverse events that have been reported in post-marketing surveillance include: ventricular arrhythmia, prolongation of QT interval, diabetes insipidus (usually nephrogenic), renal calculus, and muscle disorders including myopathy, myositis, muscle weakness and rare cases of rhabdomyolysis. Cases of vesiculobullous eruptions including erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson Syndrome have been reported. In most cases, patients were taking other medications that have been associated with toxic epidermal necrolysis or Stevens-Johnson Syndrome.

OVERDOSAGE

In controlled clinical trials performed in the United States, overdosage with FOSCAVIR was reported in 10 out of 189 patients. All 10 patients experienced adverse events and all except one made a complete recovery. One patient died after receiving a total daily dose of 12.5 g for three days instead of the intended 10.9 g. The patient suffered a grand mal seizure and became comatose. Three days later the patient expired with the cause of death listed as respiratory/cardiac arrest. The other nine patients received doses ranging from 1.14 times to 8 times their recommended doses with an average of 4 times their recommended doses. Overall, three patients had seizures, three patients had renal function impairment, four patients had paresthesias either in limbs or periorally, and five patients had documented electrolyte disturbances primarily involving calcium and phosphate.

The pattern of adverse events associated with overdose in post-marketing surveillance is consistent with the symptoms previously observed during foscarnet therapy.

There is no specific antidote for FOSCAVIR overdose. Hemodialysis and hydration may be of benefit in reducing drug plasma levels in patients who receive an overdosage of FOSCAVIR, but the effectiveness of these interventions has not been evaluated. The patient should be observed for signs and symptoms of renal impairment and electrolyte imbalance. Medical treatment should be instituted if clinically warranted.

DOSAGE AND ADMINISTRATION

CAUTION--DO NOT ADMINISTER FOSCAVIR BY RAPID OR BOLUS INTRAVENOUS INJECTION. THE TOXICITY OF FOSCAVIR MAY BE INCREASED AS A RESULT OF EXCESSIVE PLASMA LEVELS. CARE SHOULD BE TAKEN TO AVOID UNINTENTIONAL OVERDOSE BY CAREFULLY CONTROLLING THE RATE OF INFUSION. THEREFORE, AN INFUSION PUMP MUST BE USED. IN SPITE OF THE USE OF AN INFUSION PUMP, OVERDOSES HAVE OCCURRED.

ADMINISTRATION

FOSCAVIR is administered by controlled intravenous infusion, either by using a central venous line or by using a peripheral vein. The standard 24 mg/mL solution may be used with or without dilution when using a central venous catheter for infusion. When a peripheral vein catheter is used, the 24 mg/mL solution **must** be diluted to 12 mg/mL with 5% dextrose in water or with a normal saline solution prior to administration to avoid local irritation of peripheral veins. Since the dose of FOSCAVIR is calculated on the basis of body weight, it may be desirable to remove and discard any unneeded quantity from the bottle before starting with the infusion to avoid overdosage. Dilutions and/or removals of excess quantities should be accomplished under aseptic conditions. Solutions thus prepared should be used within 24 hours of first entry into a sealed bottle. *To reduce the risk of nephrotoxicity, creatinine clearance (mL/min/kg) should be calculated even if serum creatinine is within the normal range, and doses should be adjusted accordingly.*

Hydration: Hydration may reduce the risk of nephrotoxicity. It is recommended that 750-1000 mL of normal saline or 5% dextrose solution should be given prior to the first infusion of FOSCAVIR to establish diuresis. With subsequent infusions, 750-1000 mL of hydration fluid should be given with 90-120 mg/kg of FOSCAVIR, and 500 mL with 40-60 mg/kg of FOSCAVIR. Hydration fluid may need to be decreased if clinically warranted. After the first dose, the hydration fluid should be administered concurrently with each infusion of FOSCAVIR.

Compatibility With Other Solutions/Drugs: Other drugs and supplements can be administered to a patient receiving FOSCAVIR. However, care must be taken to ensure that FOSCAVIR is only administered with normal saline or 5% dextrose solution and that no other drug or supplement is administered concurrently via the same catheter. Foscarnet has been reported to be chemically incompatible with 30% dextrose, amphotericin B, and solutions containing calcium such as Ringer's lactate and TPN. Physical incompatibility with other IV drugs has also been reported including acyclovir sodium, ganciclovir, trimetrexate glucuronate, pentamidine isethionate, vancomycin, trimethoprim/sulfamethoxazole, diazepam, midazolam, digoxin, phenytoin, leucovorin, and prochlorperazine. Because of foscarnet's chelating properties, a precipitate can potentially occur when divalent cations are administered concurrently in the same catheter. Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored or contain particulate matter should not be used.

Accidental Exposure: Accidental skin and eye contact with foscarnet sodium solution may cause local irritation and burning sensation. If accidental contact occurs, the exposed area should be flushed with water.

DOSAGE

THE RECOMMENDED DOSAGE, FREQUENCY, OR INFUSION RATES SHOULD NOT BE EXCEEDED. ALL DOSES MUST BE INDIVIDUALIZED FOR PATIENTS' RENAL FUNCTION.

Induction Treatment: The recommended initial dose of FOSCAVIR for patients with normal renal function is:

- For CMV retinitis patients, either 90 mg/kg (1-1/2 to 2 hour infusion) every twelve hours or 60 mg/kg (minimum one hour infusion) every eight hours over 2-3 weeks depending on clinical response.
- For acyclovir-resistant HSV patients, 40 mg/kg (minimum one hour infusion) either every 8 or 12 hours for 2-3 weeks or until healed.

An infusion pump must be used to control the rate of infusion. Adequate hydration is recommended to establish a diuresis (see Hydration for recommendation), both prior to and during treatment to minimize renal toxicity (see WARNINGS), provided there are no clinical contraindications.

Maintenance Treatment: Following induction treatment the recommended maintenance dose of FOSCAVIR for CMV retinitis is 90 mg/kg/day to 120 mg/kg/day (individualized for renal function) given as an intravenous infusion over 2 hours. Because the superiority of the 120 mg/kg/day has not been established in controlled trials, and given the likely relationship of higher plasma foscarnet levels to toxicity, it is recommended that most patients be started on maintenance treatment with a dose of 90 mg/kg/day. Escalation to 120 mg/kg/day may be considered should early reinduction be required because of retinitis progression. Some patients who show excellent tolerance to FOSCAVIR may benefit from initiation of maintenance treatment at 120 mg/kg/day earlier in their treatment.

An infusion pump must be used to control the rate of infusion with all doses. Again, hydration to establish diuresis both prior to and during treatment is recommended to minimize renal toxicity, provided there are no clinical contraindications (see WARNINGS).

Patients who experience progression of retinitis while receiving FOSCAVIR maintenance therapy may be retreated with the induction and maintenance regimens given above or with a combination of FOSCAVIR and ganciclovir (see CLINICAL TRIALS section). **Because of physical incompatibility, FOSCAVIR and ganciclovir must NOT be mixed.**

Use in Patients with Abnormal Renal Function: FOSCAVIR should be used with caution in patients with abnormal renal function because reduced plasma clearance of foscarnet will result in elevated plasma levels (see CLINICAL PHARMACOLOGY). In addition, FOSCAVIR has the potential to further impair renal function (see WARNINGS). Safety and efficacy data for patients with baseline serum creatinine levels greater than 2.8 mg/dL or measured 24-hour creatinine clearances < 50 mL/min are limited.

Renal function must be monitored carefully at baseline and during induction and maintenance therapy with appropriate dose adjustments for FOSCAVIR as outlined below (see Dose Adjustment and PATIENT MONITORING). During FOSCAVIR therapy if creatinine clearance falls below the limits of the dosing nomograms (0.4 mL/min/kg), FOSCAVIR should be discontinued, the patient hydrated, and monitored daily until resolution of renal impairment is ensured.

Dose Adjustment: FOSCAVIR dosing must be individualized according to the patient's renal function status. Refer to Table 9 below for recommended doses and adjust the dose as indicated. Even patients with serum creatinine in the normal range may require dose adjustment; therefore, the dose should be calculated at baseline and frequently thereafter.

To use this dosing guide, actual 24-hour creatinine clearance (mL/min) must be divided by body weight (kg), or the estimated creatinine clearance in mL/min/kg can be calculated from serum creatinine (mg/dL) using the following formula (modified Cockcroft and Gault equation):

For males:

$$140 - \text{age} (\times 0.85 \text{ for females}) = \text{mL/min/kg}$$
$$\text{serum creatinine} \times 72$$

TABLE 9
FOSCAVIR DOSING GUIDE
INDUCTION

CrCl (mL/min/kg)	HSV: Equivalent to		CMV: Equivalent to	
	80 mg/kg/day total (40 mg/kg Q12h)	120 mg/kg/day total (40 mg/kg Q8h)	180 mg/kg/day total (60 mg/kg Q8h)	(90 mg/kg Q12h)
>1.4	40 Q12h	40 Q8h	60 Q8h	90 Q12h
>1.0-1.4	30 Q12h	30 Q8h	45 Q8h	70 Q12h
>0.8-1.0	20 Q12h	35 Q12h	50 Q12h	50 Q12h
>0.6-0.8	35 Q24h	25 Q12h	40 Q12h	80 Q24h
>0.5-0.6	25 Q24h	40 Q24h	60 Q24h	60 Q24h
>/=0.4-0.5	20 Q24h	35 Q24h	50 Q24h	50 Q24h
<0.4	Not Recommended	Not Recommended	Not Recommended	Not Recommended

MAINTENANCE

CrCl (mL/min/kg)	CMV: Equivalent to	
	90 mg/kg/day (once daily)	120 mg/kg/day (once daily)
>1.4	90 Q24h	120 Q24h
>1.0-1.4	70 Q24h	90 Q24h
>0.8-1.0	50 Q24h	65 Q24h
>0.6-0.8	80 Q48h	105 Q48h
>0.5-0.6	60 Q48h	80 Q48h
>/=0.4-0.5	50 Q48h	65 Q48h
<0.4	Not Recommended	Not Recommended

> means "greater than"; >/= means "greater than or equal to"; < means "less than"

PATIENT MONITORING

The majority of patients will experience some decrease in renal function due to FOSCAVIR administration. Therefore it is recommended that creatinine clearance, either measured or estimated using the modified Cockcroft and Gault equation based on serum creatinine, be determined at baseline, 2-3 times per week during induction therapy and at least every one to two weeks during maintenance therapy, with FOSCAVIR dose adjusted accordingly (see Dose Adjustment). More frequent monitoring may be required for some patients. It is also recommended that a 24-hour creatinine clearance be determined at baseline and periodically thereafter to ensure correct dosing (assuming verification of an adequate collection using creatinine index). FOSCAVIR should be discontinued if creatinine clearance drops below 0.4 mL/min/kg.

Due to FOSCAVIR's propensity to chelate divalent metal ions and alter levels of serum electrolytes, patients must be monitored closely for such changes. It is recommended that a schedule similar to that recommended for serum creatinine (see above) be used to monitor serum calcium, magnesium, potassium and phosphorus. Particular caution is advised in patients with decreased total serum calcium or other electrolyte levels before treatment, as well as in patients with neurologic or cardiac abnormalities, and in patients receiving other drugs known to influence serum calcium levels. Any clinically significant metabolic changes should be corrected. Also, patients who experience mild (e.g., perioral numbness or paresthesias) or severe (e.g., seizures) symptoms of electrolyte abnormalities should have serum electrolyte and mineral levels assessed as close in time to the event as possible.

Careful monitoring and appropriate management of electrolytes, calcium, magnesium and creatinine are of particular importance in patients with conditions that may predispose them to seizures (see WARNINGS).

HOW SUPPLIED

FOSCAVIR (foscarnet sodium) INJECTION, 24 mg/mL for intravenous infusion, is supplied in glass bottles as follows:

NDC 0186-1906-01 500 mL bottles, cases of 12

NDC 0186-1905-01 250 mL bottles, cases of 12

FOSCAVIR INJECTION should be stored at controlled room temperature, 15°-30°C (59° - 86°F), and should be protected from excessive heat (above 40°C) and from freezing. FOSCAVIR INJECTION should be used only if the bottle and seal are intact, a vacuum is present, and the solution is clear and colorless.

Rx only

Manufactured by:

Abbott Laboratories, North Chicago, IL 60064

Manufactured for:

Astra Pharmaceuticals, L.P., Wayne, PA 19087